DETAILED ACTION

The Group and/or Art Unit of your application has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1648, Examiner Foley.

Claims 1, 2, 4-18, 20-32, 34-39, 41, 42, 44-47, 49-54 and 57-67 are pending; claims 16-18, 20-32, 34-39, 41, 42, 44-47, 49-54 and 62-66 are withdrawn due to non-elected subject matter; and claims 1, 2, 4-15, 57-61 and 67 are under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on February 17, 2011 has been considered by the examiner.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, 5, 8 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodle et al. (US 5,356,633) and Metselaar et al. (Arthritis and Rheumatism. 2003; 48 (7): 2059-2066) for reasons of record.

Applicant summarizes the instantly claimed limitations and asserts that the "vesicle-forming lipids" of Woodle et al. are not water-soluble because they comprise water-insoluble hydrophobic regions.

Applicant correctly summarizes the teachings of Woodle et al. as requiring hydrophilic biocompatible polymers, such as PEG, linked to vesicle-forming lipids. However, the transitional phrase, "comprising", recited in the instant claims, does not exclude any component, such as vesicle-forming lipids, from the instant requirements in the composition. Woodle et al. teach compositions comprising a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory therapeutic agents, such as NSAIDs, see column 4, lines 9-25. The composition is formulated such that upon administration, it concentrates in a predetermined site, see column 4, lines 32-50. Therefore, the required components instantly claimed are taught by Woodle et al.

Applicant similarly asserts that the PEG-DSPE conjugate liposomes of Metselaar et al. are not water-soluble polymers, as instantly required.

A review of the teachings of Metselaar et al. in view of applicant's arguments have been fully considered, but are found unpersuasive. Woodle et al. clearly teach a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory therapeutic agents, such as NSAIDs, that concentrate at a predetermined site, see column 4, lines 9-25 and lines 32-50. Metselaar et al. is not required to teach what is already taught by Woodle et al. The teachings of Metselaar et al. are required to teach motivation for combining glucocorticoids with a PEG carrier with a reasonable expectation of success. Metselaar et al. teach incorporating glucocorticoids into PEG liposomes, see "Preparations" bridging the columns on page 2060.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate glucocorticoids of Metselaar et al. into the inflammatory treatment

formulation of Woodle et al. with a reasonable expectation of success because glucocorticoids are conventional for the treatment of arthritis; the incorporation of glucocorticoids into the formulation of Woodle et al. would have achieved rapid anti-inflammatory effects and specific accumulation at the site of inflammation; see Figures 3 and 4 on page 2063 and "Tissue Distribution" on page 2062 of Metselaar et al.

Applicant does not disagree with the assertion of obviousness to directly link an anti-inflammatory agent to a polymer since neither Metselaar et al. on page 2062 nor Woodle et al. teach linking an anti-inflammatory agent to the PEG carrier.

Applicant's arguments have been fully considered, but are found unpersuasive. According to MPEP § 2141,

> [T]he focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge. This is so regardless of whether the source of that knowledge and ability was documentary prior art, general knowledge in the art, or common sense.

In the instant case, both Woodle et al. and Metselaar et al. teach direct linkage of the lipid to the polymer, see column 7, lines 14-44 of Woodle et al. and "Preparations" bridging the columns on page 2060 of Metselaar et al. Therefore, this type of juncture between two components in a construct is clearly conventional to the ordinary skilled artisan and was of general knowledge in the art at the time the invention was made.

In addition, Metselaar et al. clearly show gradual localization and retention of liposomes at inflamed sites at 4, 20, 24 and 48 hours after injection, see Figures 2A and 2B and Woodle et al. clearly demonstrate sustained accumulation at target sites only when hydrophilic polymer-linked conjugations are used, see Figures 8B, 9, 10 and 11. Therefore, it would have been

reasonable to directly link drug and polymers to optimize therapeutic efficacy. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to directly link the anti-inflammatory drug to the carrier to ensure targeted delivery and accumulation at the inflamed areas, see "Tissue Distribution" on page 2062 of Metselaar et al. and Figures 8B, 9, 10 and 11 of Woodle et al.

Applicant asserts that on page 2065 Metselaar et al. teach away from delivering an anti-inflammatory drug that is not encapsulated within a liposome.

Applicant's arguments have been fully considered, but are found unpersuasive. Woodle et al. clearly teach a hydrophilic biocompatible polymer, polyethylene glycol (PEG), in combination with anti-inflammatory therapeutic agents, such as NSAIDs that concentrate at a predetermined site, see column 4, lines 9-25 and lines 32-50. Metselaar et al. is not required to teach what is already taught by Woodle et al. The teachings of Metselaar et al. are required to teach motivation for combining glucocorticoids with a PEG carrier with a reasonable expectation of success. Metselaar et al. teach incorporating glucocorticoids into PEG liposomes, see "Preparations" bridging the columns on page 2060.

In regard to the teachings of Woodle et al., applicant points to column 19 and points out that Woodle et al. only teach the use of liposomes with preferable "minimal leakage".

The teachings of Woodle et al. and applicant's arguments have been fully considered, but are found unpersuasive since "minimal leakage" would not be a factor for a construct comprising PEG directly linked to the anti-inflammatory agent. Woodle et al. clearly demonstrate sustained accumulation at target sites only when hydrophilic polymer-linked conjugations are used, see Figures 8B, 9, 10 and 11. Therefore, it would have been reasonable to directly link drug and

polymers to optimize therapeutic efficacy. In addition, one of ordinary skill in the art at the time the invention was made would have been motivated to directly link the anti-inflammatory drug to the carrier to ensure targeted delivery and accumulation at the inflamed areas, see "Tissue Distribution" on page 2062 of Metselaar et al. and Figures 8B, 9, 10 and 11 of Woodle et al.

Claims 2, 4, 6, 7, 9-14 and 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodle et al. and Metselaar et al. as applied to claims 1, 4, 5, 8 and 15 above, and further in view of Omelyanenko et al. (Journal of Controlled Release. 1998; 53: 25-37) and Smolen et al. (Nature Reviews. June, 2003; 2: 473-488) for reasons of record.

Applicant states that Omelyanenko et al. is only concerned with the delivery of chemotherapeutic agents to cancer cells. Applicant further points out that on pages 33-35, Omelyanenko et al. also teach that polymer-conjugated-chemotherapeutic drugs are more slowly delivered to cells than free drugs.

Applicant's arguments in view of the teachings of Omelyanenko et al. have been fully considered, but are found unpersuasive. As pointed out by applicant, Omelyanenko et al. do indeed teach slowed delivery of drug-conjugated-HPMA polymers. However, this observation lends itself to the fact that HPMA-bound-drugs increase drug concentrations inside cells, see Figures 9 and 10 of Omelyanenko et al. Therefore, Omelyanenko et al. clearly shows that drugs are efficiently delivered and accumulate in cellular targets when they are conjugated to the hydrophilic polymer, HPMA. Cellular mechanisms involved in HPMA drug trafficking would be consistent with any conjugated drug and is not limited to chemotherapeutic agents. Drug accumulation data of Omelyanenko et al. is consistent with the data of Metselaar et al. and Woodle et al. Metselaar et al. clearly show gradual localization and retention of PEG liposomes

at inflamed sites at 4, 20, 24 and 48 hours after injection, see Figures 2A and 2B and Woodle et al. clearly demonstrate sustained accumulation at target sites only when hydrophilic polymer-linked conjugations are used, see Figures 8B, 9, 10 and 11. Therefore, the prior art clearly indicates that drug efficacy is not established by how fast the drug is delivered, but by how efficiently the drugs are delivered to the target and how much drug accumulates at the intended sites.

Applicant asserts that Smolen et al. do not ameliorate the deficiencies of Woodle et al., Metselaar et al. and Omelyanenko et al. However, since there are no deficiencies persuasively identified for Smolen et al. to ameliorate, the teachings of Smolen et al. remain applicable.

New Grounds of Rejection

Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Woodle et al., Metselaar et al., Omelyanenko et al. and Smolen et al. as applied to claims 1, 4, 5, 8 and 15 above, and further in view of Russel-Jones et al. (USPgPub 2006/0127310).

See the teachings of Woodle et al., Metselaar et al., Omelyanenko et al. and Smolen et al. above. None of the references teach or suggest using a cleavable spacer comprising hydrazone.

However, Russell-Jones et al. do, see paragraph [0088].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the hydrazone linker of Russel-Jones et al. since it is a conventional linker for joining polymers to drug, see paragraph [0088]. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using the hydrazone linker of Russell-Jones et al. in the conjugate of Woodle et al., Metselaar

et al., Omelyanenko et al. and Smolen et al. above since Russell-Jones et al. teach delivering HPMA polymer – anti-inflammatory drug conjugates, see Examples 33 and 36.

Previous Grounds of Rejection

Claims 1, 2 and 4-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. (Bioconjugate Chemistry. 2003; 14: 853-859) and Metselaar et al. (Arthritis and Rheumatism. 2003; 48 (7): 2059-2066) for reasons of record.

Applicant argues that Wang et al. do not teach or suggest the administration of anti-inflammatory agents, but discusses the delivery of bone therapeutic agents that bind bone outside of joints. Applicant further argues that Metselaar et al. only teach the use of liposomes to deliver anti-inflammatory agents. Applicant asserts that Metselaar et al. teach away from delivering an anti-inflammatory drug that is not encapsulated within a liposome because Metselaar et al. teach that free-anti-inflammatory drug degrades on page 2065.

Applicant's arguments have been fully considered, but are found unpersuasive. Metselaar et al. is not required to teach what is already taught by Wang et al. The teachings of Metselaar et al. are required to teach motivation for combining glucocorticoids with a PEG carrier with a reasonable expectation of success. Metselaar et al. teach incorporating glucocorticoids into PEG liposomes, see "Preparations" bridging the columns on page 2060.

Wang et al. teach water-soluble HPMA copolymer conjugates comprising bone-targeting compounds, alendronate and aspartic acid peptide and bio-assay label, FITC. The bone therapeutics were covalently attached to the HPMA copolymer carrier by acid or enzymatic cleavable and uncleavable spacer (-GG-). See the abstract, the paragraph bridging pages 853-

854, as well as the second and third paragraphs of the second column on page 854. As stated in the previous Office action, Wang et al. do not teach delivering therapeutic agents.

Metselaar et al. teach incorporating glucocorticoids into PEG liposomes, see "Preparations" bridging the columns on page 2060.

One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate glucocorticoids of Metselaar et al. into the HPMA copolymer conjugate of Wang et al. to deliver the arthritis treatment agent specifically to the targeted tissue. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for incorporating glucocorticoids into the HPMA copolymer conjugate of Wang et al. because Wang et al. teach an additional copolymer PEG conjugate and the bone-targeting capability of the conjugates of Wang et al. would be advantageous for the treatment of arthritis, see "Tissue distribution" on page 2062 of Metselaar et al. Therefore, since there is motivation to attach the anti-inflammatory drugs of Metselaar et al. to Wang et al. with a reasonable expectation of success, the degradation of the anti-inflammatory drugs discussed by Metselaar et al. on page 2065 would be a moot point.

Claims 57-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al. and Metselaar et al. as applied to claims 1, 2 and 4-15 above, and further in view of Smolen et al. and Omelyanenko et al. for reasons of record.

Applicant states that Omelyanenko et al. is only concerned with the delivery of chemotherapeutic agents to cancer cells. Applicant further points out that on pages 33-35, Omelyanenko et al. also teach that polymer-conjugated-chemotherapeutic drugs are more slowly delivered to cells than free drugs.

Applicant's arguments in view of the teachings of Omelyanenko et al. have been fully considered, but are found unpersuasive. As pointed out by applicant, Omelyanenko et al. do indeed teach slowed delivery of drug-conjugated-HPMA polymers. However, this observation lends itself to the fact that HPMA-bound-drugs increase drug concentrations inside cells, see Figures 9 and 10 of Omelyanenko et al. Therefore, Omelyanenko et al. clearly shows that drugs are efficiently delivered and accumulate in cellular targets when they are conjugated to the hydrophilic polymer, HPMA. Cellular mechanisms involved in HPMA drug trafficking would be consistent with any conjugated drug and is not limited to chemotherapeutic agents. Drug accumulation data of Omelyanenko et al. is consistent with the data of Metselaar et al.

Metselaar et al. clearly show gradual localization and retention of PEG liposomes at inflamed sites at 4, 20, 24 and 48 hours after injection, see Figures 2A and 2B. Therefore, the prior art clearly indicates that drug efficacy is not established by how fast the drug is delivered, but by how efficiently the drugs are delivered to the target and how much drug accumulates at the intended sites.

Applicant asserts that Smolen et al. do not ameliorate the deficiencies of Wang et al., Metselaar et al. and Omelyanenko et al. However, since there are no deficiencies persuasively identified for Smolen et al. to ameliorate, the teachings of Smolen et al. remain applicable.

New Grounds of Rejection

Claim 67 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al., Metselaar et al., Omelyanenko et al. and Smolen et al. as applied to claims 1, 2, 4-15 and 57-61 above, and further in view of Russel-Jones et al. (USPgPub 2006/0127310).

See the teachings of Wang et al., Metselaar et al., Omelyanenko et al. and Smolen et al. above. None of the references teach or suggest using a cleavable spacer comprising hydrazone.

However, Russell-Jones et al. do, see paragraph [0088].

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have incorporated the hydrazone linker of Russel-Jones et al. since it is a conventional linker for joining polymers to drug, see paragraph [0088]. One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success for using the hydrazone linker of Russell-Jones et al. in the conjugate of Wang et al., Metselaar et al., Omelyanenko et al. and Smolen et al. above since Russell-Jones et al. teach delivering HPMA polymer – anti-inflammatory drug conjugates, see Examples 33 and 36.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHANON A. FOLEY whose telephone number is (571)272-0898. The examiner can normally be reached on flex, generally M-F 7AM - 3 PM, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas can be reached on (571) 272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SHANON A. FOLEY/
Primary Examiner
Art Unit 1648